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Oxime–Palladacycle-Catalyzed Suzuki–Miyaura Arylation and Alkenylation of Aryl Imidazolesulfonates under Aqueous and Phosphane-Free Conditions

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Dedicated to the memory of Professor Balbino Mancheño

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Aryl and hetaroaryl imidazole-1-sulfonates are efficiently arylated and alkenylated with aryl- and alkenylboronic acids and potassium trifluoroborates by using 0.5 mol-% palladacycles **1** or $Pd(OAc)_2$ at 110 °C under aqueous and phosphane-free conditions. Reactions can be performed by using conventional or microwave heating, leading to biaryls, stilbenes, and alkenylarenes in good to high yields, and high regio- and diastereoselectivities. The optimized methodology allows in situ phenol sulfonylation and one-pot Suzuki arylation or alkenylation as well as orthogonal functionalization of halogen-containing aryl imidazolesulfonates.

Introduction

The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction constitutes one of the most powerful carbon–carbon bond-forming transformations.[1] Although cross-couplings of aryl halides are most common, significant efforts are underway to make the Suzuki coupling a greener chemical process by using inexpensive, readily available, and less toxic hydroxylated arene derivatives[2,3] as electrophiles.[4] Traditionally, the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of enols, phenols, and hydroxylated arenes has usually involved their prior transformation into triflates due to the superior performance of these derivatives as electrophilic partners.[5] However, triflates are substrates with limited stability. Thus, a number of recent studies have shown the ability of other groups, such as mesylates and sulfonates,[6,7] carbamates,[8] carbonates,[8a] carboxylates,[7a,9,10] methyl ethers,[11] phosphonium salts,[12,13] phosphoramides,[14] phosphates,[15,16] borates,[17] and *N*,*N*-dialkyl-*O*-sulfamates,[8a,8c,18] to participate in the Suzuki reaction (Scheme 1).

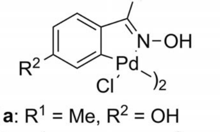
$$\text{R–OX} \quad + \quad \text{R'BX'} \xrightarrow[\text{phosphane ligand}]{\text{Ni or Pd catalyst}} \text{R–R'}$$

R = aryl, heteroaryl, alkenyl
OX = OMe, OCOR'', OCO_2R'', OSO_2R'', $OCONR''_2$, $OSO_2NR''_2$, $OP(O)(NR''_2)_2$, $OP(O)(OR'')_2$, $OP^+(NR''_2)_3$,
R' = aryl, heteroaryl, alkenyl
BX' = $B(OH)_2$, BF_3K

Scheme 1. Suzuki C–O activation catalyzed by Ni or Pd.

These electrophiles have usually been employed in the synthesis of biaryls by using high loadings of nickel catalysts in the presence of phosphane ligands. Except for mesylates and tosylates, palladium catalysis has not been used so often in the Suzuki coupling of phenol derivatives, with the presence of ancillary phosphane ligands being mandatory for successful coupling. For instance, aryl imidazolesulfonates have been demonstrated to be efficient electrophilic coupling partners in the Suzuki reaction with arylboronic acids by employing bidentate phosphanes 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) and BINAP, under high catalyst loadings (5–10 mol-% Pd).[19,20]

The Suzuki coupling of the hydroxylated arene derivatives mentioned above has been largely developed by using traditional organic solvents, which greatly reduces the environmental sustainability of the process.[21] In our research group, the Suzuki reaction has been studied during the past decade by using oxime–palladacycles **1** (Figure 1) or $Pd(OAc)_2$ as efficient precatalysts for the coupling of vinyl



1a: R^1 = Me, R^2 = OH
1b: R^1 = 4-ClC_6H_4, R^2 = Cl

Figure 1. Oxime–palladacycle catalysts.

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and aryl halides with boronic acids and potassium trifluoroborates in organic and aqueous solvents.[22–25]

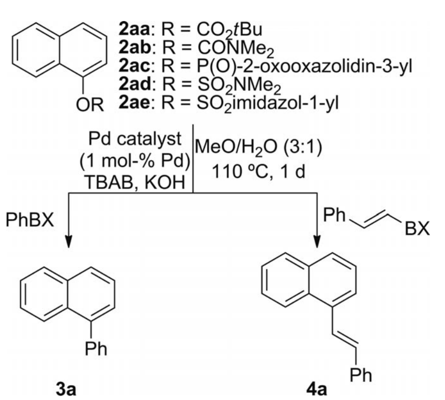
Regarding C–O activation, we have recently disclosed in a preliminary communication, a general phosphane-free oxime–palladacycle-catalyzed Suzuki cross-coupling reaction of electron-rich, electron-poor, and hindered aryl imidazolesulfonates with arylboronic acids and potassium aryltrifluoroborates under aqueous and low catalyst loading conditions.[26] Herein, we report a full account of the biaryl synthesis as well as the results obtained for the alkenylation of aryl and heteroaryl imidazole-1-sulfonates under aqueous conditions by using conventional or microwave heating.[27]

Results and Discussion

Initial Suzuki cross-coupling studies were carried out with 1-naphthol derivatives **2** (Table 1). The cross-coupling of **2** (1 equiv.) with phenylboronic acid (1.5 equiv.) was initially performed by using catalyst **1a**[28] (1 mol-% Pd) and KOH (2 equiv.) as base in a 3:1 MeOH/H_2O mixture as solvent in the presence of tetra-*n*-butylammonium bromide (TBAB; 20 mol-%) as phase-transfer agent at 110 °C. As depicted in Table 1 (Entries 1–5), only imidazolesulfonate derivative **2ae** showed reactivity under these conditions, affording 1-phenylnaphthalene (**3a**) in 67% isolated yield (Table 1, Entry 5).[29] Once it was demonstrated that the imidazole-1-sulfonate was the best electrophile in the process, an optimization of the reaction conditions was carried out. No reaction took place when the coupling was performed in aqueous acetone or in neat water (Table 1, Entries 6 and 7). Regarding catalysts, $Pd(OAc)_2$ afforded a higher yield (84%) in the reaction (compare Table 1, Entries 5 and 8). To our surprise, the yield was improved substantially (99%) when palladacycle **1b**, a catalyst that usually performs better in organic solvents,[23] was used (Table 1, Entry 9). In the presence of catalyst **1b**, the reaction could also be performed under microwave irradiation conditions (40 W irradiation to heat to 110 °C and maintained at this temperature for 30 min), affording compound **3a** in quantitative yield after this short time (Table 1, Entry 10). The optimized results obtained with different boron electrophiles are shown in Entries 11–15. Potassium phenyltrifluoroborate afforded compound **3a** in 89% isolated yield by using catalyst **1a** (Table 1, Entry 11). With this nucleophile, catalyst **1b** and $Pd(OAc)_2$ were less effective than **1a**, affording compound **3a** in 45 and 10% yield, respectively (Table 1, Entries 12 and 13). Low yields were also obtained after 2 d when imidazolesulfonate **2ae** was treated with phenylboronic acid *N*-methyliminodiacetate (MIDA) ester (50%; Table 1, Entry 14) and phenylboronic acid pinacol ester (39%; Table 1, Entry 15).

The alkenylation of **2ae** with styrylboron nucleophiles followed a trend similar to that observed in the arylation cross-coupling. Good yields were obtained for both boronic acids and potassium trifluoroborates, and were usually higher when the reaction was carried out under microwave irradiation (Table 1, Entries 16–22). Palladium(II) acetate also showed better activity under microwave irradiation than under conventional heating, although **4a** was obtained in lower yields than when palladacycle **1b** was used (compare Table 1, Entries 16 and 17 with 18 and 19). Finally, use of oxime–palladacycle **1a** afforded **4a** in 74% yield under microwave irradiation; a result that confirmed palladacycle **1b** was also the most efficient catalyst for the alkenylation process (compare Table 1, Entries 17 and 20).

Table 1. Reaction conditions study.[a]



Entry	2	RBX	Catalyst	Product, Yield [%][b]
1	**2aa**	$PhB(OH)_2$	**1a**	**3a**, < 5
2	**2ab**	$PhB(OH)_2$	**1a**	**3a**, < 5
3	**2ac**	$PhB(OH)_2$	**1a**	**3a**, < 5
4	**2ad**	$PhB(OH)_2$	**1a**	**3a**, < 5
5	**2ae**	$PhB(OH)_2$	**1a**	**3a**, 67
6	**2ae**	$PhB(OH)_2$	**1a**[c]	**3a**, < 5
7	**2ae**	$PhB(OH)_2$	**1a**[d]	**3a**, < 5
8	**2ae**	$PhB(OH)_2$	$Pd(OAc)_2$	**3a**, 84
9	**2ae**	$PhB(OH)_2$	**1b**	**3a**, > 99
10	**2ae**	$PhB(OH)_2$	**1b**	**3a**, > 99[e]
11	**2ae**	$PhBF_3K$	**1a**	**3a**, 89
12	**2ae**	$PhBF_3K$	**1b**	**3a**, 45
13	**2ae**	$PhBF_3K$	$Pd(OAc)_2$	**3a**, 10
14	**2ae**	$PhB[(OCOCH_2)_2NMe]_2$	**1a**	**3a**, 50[f]
15	**2ae**	$PhB[\{OC(Me)_2\}]_2$	**1b**	**3a**, 39[f]
16	**2ae**	(*E*)-PhCH=CHB$(OH)_2$	**1b**	**4a**, 72
17	**2ae**	(*E*)-PhCH=CHB$(OH)_2$	**1b**	**4a**, 85[e]
18	**2ae**	(*E*)-PhCH=CHB$(OH)_2$	$Pd(OAc)_2$	**4a**, 15
19	**2ae**	(*E*)-PhCH=CHB$(OH)_2$	$Pd(OAc)_2$	**4a**, 65[e]
20	**2ae**	(*E*)-PhCH=CHB$(OH)_2$	**1a**	**4a**, 74[e]
21	**2ae**	(*E*)-PhCH=CHBF_3K	**1b**	**4a**, 72[e]
22	**2ae**	(*E*)-PhCH=CHBF_3K	**1b**	**4a**, 70

[a] Reaction conditions: Pd catalyst (1 mol-% Pd), **2** (0.1 mmol), RBX (0.15 mmol), TBAB (20 mol-%), KOH (0.2 mmol), MeOH/H_2O (3:1), 110 °C, 24 h. [b] Isolated yield after flash chromatography. [c] Reaction solvent: Me_2CO/H_2O (3:2). [d] Reaction solvent: H_2O. [e] Reaction performed under microwave irradiation (40 W, 110 °C, 30 min). [f] Reaction time: 2 d.

The scope of this methodology was then examined under the optimized reaction conditions. Initially, the coupling of a range of arylboronic acids and potassium aryltrifluoroborates with naphthalen-1-yl-1*H*-imidazole-1-sulfonate (**2ae**) was studied by using conventional (110 °C, 24 h) and microwave heating (40 W, 110 °C, 30 min). As depicted in

Table 2. Pd-catalyzed Suzuki arylations of **2ae**.[a]

2ae **3**

Entry	ArBX	1	3	Δ Yield [%][b,c]	MW yield [%][b,d]
1	$PhB(OH)_2$	**1a**	**3a**	67	76
2	$PhB(OH)_2$	**1b**	**3a**	> 99	100
3	$PhBF_3K$	**1a**	**3a**	89	89
4	$PhBF_3K$	**1b**	**3a**	45	88
5	$4\text{-}MeC_6H_4B(OH)_2$	**1a**	**3b**	90	79
6	$4\text{-}MeC_6H_4B(OH)_2$	**1b**	**3b**	76	95
7	$4\text{-}MeC_6H_4BF_3K$	**1a**	**3b**	61	70
8	$4\text{-}MeC_6H_4BF_3K$	**1b**	**3b**	72	82
9	$4\text{-}MeOC_6H_4B(OH)_2$	**1b**	**3c**	75	90
10	$4\text{-}CF_3C_6H_4B(OH)_2$	**1b**	**3d**	66	79
11	$4\text{-}CF_3C_6H_4BF_3K$	**1b**	**3d**	64	72
12	3-pyridylBF_3K	**1b**	**3e**	69	73
13	3-thienylBF_3K	**1b**	**3f**	55	69

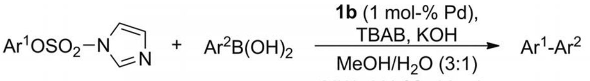
[a] Reaction conditions: Pd catalyst (1 mol-% Pd), **2ae** (0.1 mmol), ArBX (0.15 mmol), TBAB (20 mol-%), KOH (0.2 mmol). [b] Isolated yield after flash chromatography. [c] Reaction performed at 110 °C for 24 h. [d] Reaction performed under microwave (MW) irradiation (40 W, 110 °C, 30 min).

Table 2, biaryl derivatives **3a**–**f** were isolated in good to excellent yields, which were generally higher for boronic acids than for potassium trifluoroborates, and also proceeded better under microwave irradiation than with conventional heating.

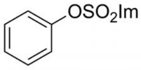
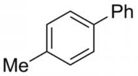
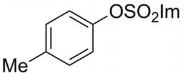
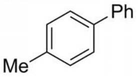
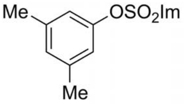
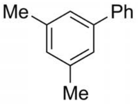
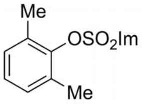
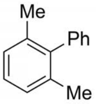
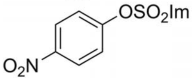
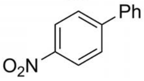
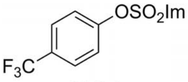
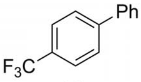
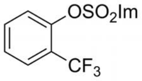
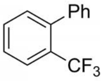
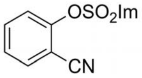
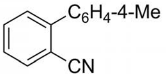
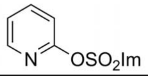
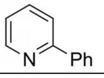
With respect to the catalyst, use of palladacycle **1b** usually afforded better results than **1a**, although no clear correlation between the catalyst and the boron source could be established from parallel experiments. Thus, further studies on the reaction scope and utility of the method were always optimized with respect to the catalyst. Electron-donating (Table 2, Entries 5–9) and electron-withdrawing groups (Table 2, Entries 10 and 11) on the phenyl ring of the nucleophile had little impact on the efficiency of the reaction, although lower yields (64–79 %) were observed for the latter. Finally, heterocyclic potassium pyrid-3-yl- and thien-3-yltrifluoroborates also showed good reactivity in this process, affording compounds **3e** and **3f** in 73 and 69 % isolated yields, respectively, by using microwave irradiation (Table 2, Entries 12 and 13).

Regarding the electrophilic component (Table 3), high isolated yields (72–96 %) were obtained in the microwave-assisted **1b**-catalyzed cross-coupling of arylboronic acids with neutral, electron-rich, and electron-poor phenyl imidazolesulfonates (Table 3, Entries 1–8). For comparison,

Table 3. Pd-catalyzed Suzuki arylation of **2**.



2 **3**

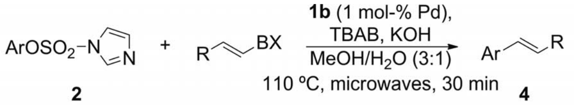
Entry	Ar^1OSO_2Im	2	$Ar^2B(OH)_2$	3	Product	Yield (%)[a]
1		**2be**	$4\text{-}MeC_6H_4B(OH)_2$	**3g**		96 (80)
2		**2ce**	$PhB(OH)_2$	**3g**		90 (90)
3		**2de**	$PhB(OH)_2$	**3h**		83 (85)
4		**2ee**	$PhB(OH)_2$	**3i**		72 (53)
5		**2fe**	$PhB(OH)_2$	**3j**		96
6		**2ge**	$PhB(OH)_2$	**3k**		90 (81)
7		**2he**	$PhB(OH)_2$	**3l**		83 (78)
8		**2ie**	$4\text{-}MeC_6H_4B(OH)_2$	**3m**		92
9		**2je**	$PhB(OH)_2$	**3n**		72

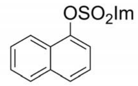
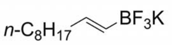
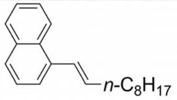
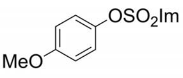
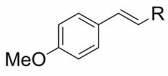
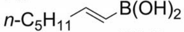
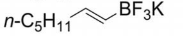
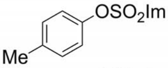
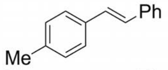
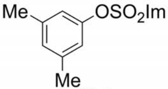
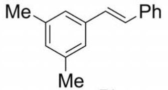
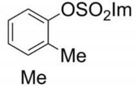
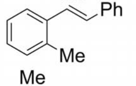
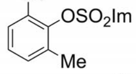
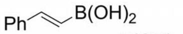
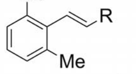
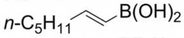
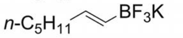
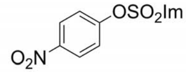
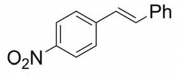
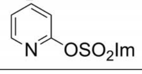
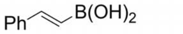
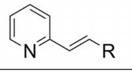
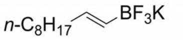
[a] Isolated yield after flash chromatography. The isolated yield under conventional thermal heating (110 °C, 24 h) is given in parentheses.

some of the cross-coupling reactions were also carried out by using conventional heating, affording similar or lower yields (with longer reaction times) under otherwise identical reaction conditions (Table 3, entries 1–4 and 6, 7). The process was also effective for the coupling of sterically hindered electrophiles such as 3,5-dimethylphenyl 1*H*-imidazole-1-sulfonate (**2ee**), 2-(trifluoromethyl)phenyl 1*H*-imidazole-1-sulfonate (**2he**), and 2-cyanophenyl 1*H*-imidazole-1-sulfonate (**2ie**) (Table 3, Entries 4, 7, and 8). In all these examples, the efficiency of the microwave irradiation was clearly demonstrated, in particular, with the sterically demanding imidazolesulfonate **2ee**, which afforded 3,5-dimethyl-1,1′-biphenyl (**3i**) in 72% yield (Table 3, Entry 4). The result illustrated in Entry 8 was especially attractive, because the obtained product, 2-cyano-4′-methylbiphenyl (**3m**), is a key intermediate in the synthesis of angiotensin II receptor antagonists that are used for the treatment of hypertension.[30] Finally, heterocyclic 2-phenylpyridine (**3n**) could also be prepared in a good isolated yield (72%) under aqueous conditions from pyridin-2-yl 1*H*-imidazole-1-sulfonate (**2je**) and phenylboronic acid (Table 3, Entry 9).

Concurrent with the above substrate scope studies on the synthesis of biaryl derivatives from aryl imidazolesulfonates, the Pd-catalyzed alkenylation of these electrophiles under aqueous conditions was then targeted.[31] Thus, a range of aryl imidazolesulfonates were cross-coupled with various β-aryl- and β-alkyl-substituted alkenylboronic acids and potassium trifluoroborates under the optimized protocol (Table 1, Entry 17) by using microwave irradiation (Table 4). In general, good isolated yields (62–93%) were obtained for the regio- and stereoselective synthesis of stilbene and styrene derivatives **4**, regardless of which nucleophile was employed. The coupling of naphthalen-1-yl 1*H*-imidazole-1-sulfonate (**2ae**) with potassium *trans*-decen-1-yltrifluoroborate afforded the corresponding *trans*-1-(dec-1-en-1-yl)naphthalene (**4b**) in 88% yield (Table 4, Entry 1). We also found that deactivated phenyl imidazole-1-sulfonates, such as those derived from 4-methoxyphenol (Table 4, Entries 2–4), 4-methylphenol (Table 4, Entry 5), and 3,5-dimethylphenol (Table 4, Entry 6), were successfully alkenylated to yield compounds **4c**–**f** in good to excellent yields (77–92%). Challenging electrophiles, such as the sterically hindered and electron-rich *o*-tolyl 1*H*-imidazole-1-sulfonate (**2le**) and 2,6-dimethylphenyl 1*H*-imidazole-1-sulfonate (**2ee**), were also successfully alkenylated with *trans*-styrylboronic acid, *trans*-hept-1-en-1-ylboronic acid, and potassium *trans*-hept-1-en-1-yltrifluoroborate to afford compounds **4g**, **4h**, and **4i**, respectively, in yields ranging from 62 to 90% (Table 4, Entries 7–10). The optimized reaction conditions were also shown to be useful for the coupling of electron-deficient electrophiles, with 4-nitrostilbene being obtained in 93% yield from the coupling of *trans*-styrylboronic acid and 4-nitrophenyl 1*H*-imidazole-1-sulfonate (**2fe**) (Table 4, Entry 11). Finally, alkenylation of heterocyclic pyridin-2-yl 1*H*-imidazole-1-sulfonate (**2je**) with *trans*-styrylboronic acid and potassium *trans*-decen-1-yltri-

Table 4. Pd-catalyzed Suzuki alkenylation of **2**.

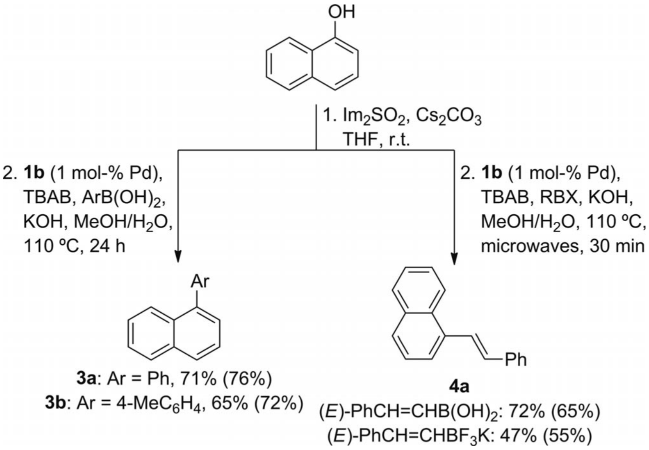


Entry	$ArOSO_2Im$	2	RCH=CHBX	Product	4	Yield (%)[a]
1		**2ae**			**4b**	88
2		**2ke**			**4c**, R = Ph	87
3		**2ke**			**4d**, R = n-C_5H_{11}	92
4		**2ke**			**4d**, R = n-C_5H_{11}	77
5		**2ce**			**4e**	81
6		**2de**			**4f**	81
7		**2le**			**4g**	73
8		**2ee**			**4h**, R = Ph	62
9		**2ee**			**4i**, R = n-C_5H_{11}	90
10		**2ee**			**4i**, R = n-C_5H_{11}	75
11		**2fe**			**4j**	93
12		**2je**			**4k**, R = Ph	65
13		**2je**			**4l**, R = n-C_8H_{17}	88

[a] Isolated yield after flash chromatography.

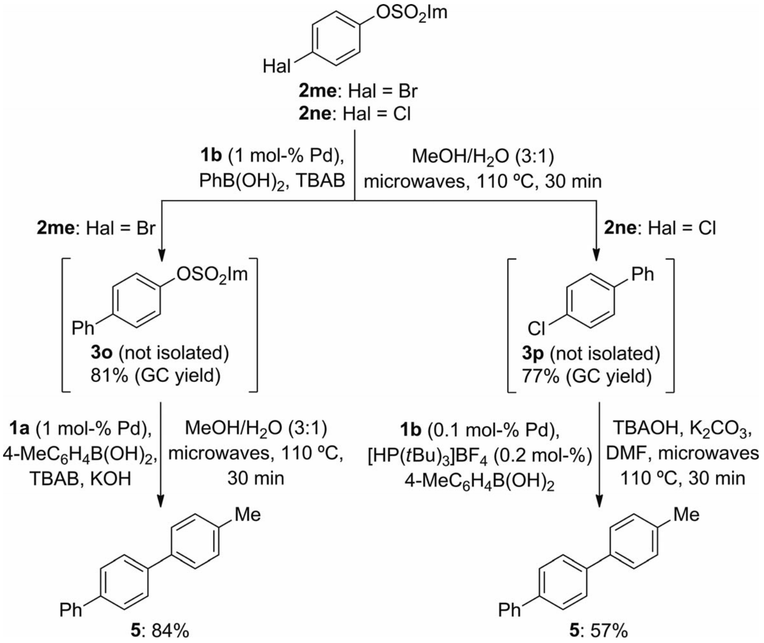
fluoroborate afforded pyridines **4k** and **4l** in 65 and 88% yield, respectively (Table 4, entries 12 and 13).

Because the synthesis of imidazolesulfonates typically proceeded quantitatively and with minimal byproduct formation, we decided to carry out a one-pot sulfonylation/Suzuki cross-coupling sequence employing 1-naphthol as starting material (Scheme 2). The in situ activation of 1-naphthol was performed by reaction with 1,1′-sufonyldiimidazole in tetrahydrofuran (THF) at room temperature by using cesium carbonate as base. Once naphthalen-1-yl 1*H*-imidazole-1-sulfonate (**2ae**) was formed (reaction monitored by TLC), the one-pot cross-coupling with a range of aryl- and styrylboronic acids and potassium trifluoroborates was carried out as depicted in Scheme 2. Both one-pot sulfonylation/arylation and sulfonylation/alkenylation reactions afforded the corresponding coupled products **3a**, **3b**, and **4a** with yields in the same range as those obtained in the stepwise process.



Scheme 2. One-pot sulfonylation/cross-coupling sequence. Isolated yield for the stepwise process given in parentheses.

Within a bifunctional starting material, orthogonal reactivity allows the chemoselective targeting of one of the two reactive centers, both of which are capable of undergoing the same chemical transformation. In Suzuki cross-coupling chemistry, the reactivity of either the electrophilic sites or the boron reagents can be modulated to carry out orthogonal functionalization.[32,33] With respect to the electrophile, orthogonal reaction strategies have been reported that take advantage of the differences in bond enthalpies of the C–I, C–Br, C–Cl, and C–O bonds. The reactivity differences between the C–O imidazolesulfonate bond and the C–Br and C–Cl bonds facilitated the microwave-promoted orthogonal cross-coupling with arylboronic acids of the halo-containing bifunctional compounds **2me** and **2ne** in a highly chemoselective fashion (Scheme 3).[34] Thus, 1,1′-biphenyl-4-yl 1*H*-imidazole-1-sulfonate (**3o**), obtained from **2me** by a **1b**-catalyzed coupling with phenylboronic acid through C–Br activation, was subsequently submitted to the **1a**-catalyzed Suzuki coupling with 4-tolylboronic acid under aqueous conditions to afford 4-methyl-1,1′:4′,1′′-terphenyl (**5**) in 84% overall isolated yield (Scheme 3). On the other hand, **5** was also synthesized from 4-chlorophenyl 1*H*-imidazole-1-sulfonate (**2ne**) in 57% overall solated yield, by initial Suzuki coupling with phenylboronic acid followed by coupling with 4-tolylboronic acid catalyzed by palladacycle **1b** (0.1 mol-% Pd) in the presence of [HP(tBu)$_3$]BF$_4$ (0.2 mol-%) in *N*,*N*-dimethylformamide (DMF).[35]



Scheme 3. Orthogonal Suzuki–Miyaura cross-coupling of halogen-containing aryl imidazolesulfonates.

Conclusions

We have disclosed a general, phosphane-free oxime–palladacycle-catalyzed Suzuki cross-coupling reaction of electron-rich, electron-poor, and sterically hindered aryl imidazolesulfonates with aryl- and alkenylboronic acids and potassium trifluoroborates under aqueous conditions. The reaction, which can be performed under conventional heating or microwave irradiation, has been optimized for use with only 1 mol-% Pd in bench-stable palladacycles **1**. Furthermore, this methodology allows in situ phenol sulfonylation and one-pot Suzuki arylation and alkenylation. Furthermore, by taking advantage of the different reactivity patterns shown by the ArC–Br, ArC–Cl, and ArC–OSO$_2$Im bonds under the reaction conditions studied, orthogonal functionalization of bifunctionalized aryl derivatives through the Suzuki–Miyaura coupling has been demonstrated.

Experimental Section

Typical Experimental Procedure for the Arylation Coupling under Microwave Heating: To a 10 mL microwave vessel charged with **2ae** (0.027 g, 0.1 mmol), phenylboronic acid (0.018 g, 0.15 mmol), KOH (0.011 g, 0.2 mmol), TBAB (0.016 g, 0.05 mmol), and catalyst **1b** (0.00041 g, 1 mol-% Pd), an MeOH/H$_2$O mixture (3:1, 2 mL) was added. The vessel was then sealed with a pressure lock, and the mixture was heated in air at 110 °C by microwave irradiation (40 W), keeping this temperature in a CEM Discover microwave reactor for 20 min. After cooling to room temperature, the reaction mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with H$_2$O (3 × 10 mL), dried with MgSO$_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexane/EtOAc, 3:1) to obtain pure **3a** (0.019 g, 100 %).

Supporting Information (see footnote on the first page of this article): Experimental procedures for the synthesis of compounds **2** and for cross-coupling reactions as well as spectroscopic data for all the synthesized products.

Acknowledgments

Financial support from the Spanish Ministry (Projects CTQ2007-62771/BQU, CTQ2010-20387, Consolider INGENIO 2010 CSD2007-00006, and FEDER), from the Generalitat Valenciana (PROMETEO/2009/038), and the University of Alicante is acknowledged.

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